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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/553,978	04/20/2000	Paul L. Gourley	SD-6450/S-92.434	4921

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Sandia National Laboratories
Patent & Licensing Office MS0161
PO Box 5800
Albuquerque, NM 87185-0161

EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 07/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/553,978	GOURLEY, PAUL L.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-7 have been amended. Claims 8 and 9 have been added. Claims 1-9 are under consideration.

2. Text of Title 35, US Code not found in this action can be found in a prior action.

3. In the previous action it was stated that claims 1-5 drawn to the discernment of G1 cells versus G2 cells will be given the instant priority date of April 20, 2000 because there is no written description for a method of detecting cancer, or a method of a method of determining the phase of cells in the cell cycle, both methods dependent upon the discernment of G1 cells versus G2 cells within the laser biocavity in the priority applications. It is noted that all the claims as amended, and all the newly added claims deal are reliant upon the determination of the phase of cells in the cell cycle, and thus all claims will have the effective priority date of April 20, 2000.

4. Claim 5 is objected to because of the following informalities: the typographical error of "G1 "phases" rather than G1 phase. . Appropriate correction is required.

5. Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in the recitation of "categorizing a phase of the cell using the wavelength shift of the laser biocavity"; claim 4 recites "determining a phase of the cell using the wavelength shift"; claim 5 is vague and indefinite in the recitation of "categorizing the phase of each of the plurality of cells as being in G1 phase or G2 phase using the wavelength shift"; claim 8 is vague and indefinite in the recitation of "categorizing a phase of the cell of the type to be categorized using the wavelength shift of the laser wavelength of the laser biocavity"; claim 7 is vague and indefinite in the recitation of "determining a phase of the cell in a cell growth cycle using the biomolecular concentration". These steps of claims 1, 4, 5, 7 and 8 in reference to the wavelength shift and the bimolecular concentration, are not active method steps because "using" is not a description of a specific action.

It is unclear how providing "an indication of cancer" as recited in claim 5 further modifies the method objective of claim 54, drawn to a method of determining the phase of cells. Claim 6 is vague and indefinite in the recitation of "determining by means of the wavelength shift a biomolecular concentration of the cell" which is not an active method step because "by means of" is not a description of a specific action.

It is unclear how determining the ratio of a percentage of cells in the G2 phase versus a percentage of cells in G2 phase in a non-cancerous cell population in claim 7 further limits the method objective of claim 6 drawn to determining bimolecular concentration.

Claim 8 is vague and indefinite in the recitation of "increased growth rate" without reference to the growth rate it is relative to. It is unclear how the final method step resulting in a measurement of a cell growth rate relates to the method objective of detecting an increased cell growth rate. Further it is unclear how "no cells of a type to be categorized" differs from "no cells". Thus, it is unclear if the metes and bounds would permit a microchannel containing other cells of a type which will not be categorized. Claim 8 recites "first wavelength distribution" which lacks antecedent basis within the claim.

Claim 9 recites "second wavelength distribution" which lacks antecedent basis with clam 9 and claim 8. It is also unclear how the measurement of the cell growth rate as recited in claim 9 satisfies the method objective of claim 8 which is drawn to detecting an increased growth rate.

The metes and bounds of "biomolecular" concentration as recited in claims 6 and 7 cannot be determined. The specification provides no limiting definition of what a "bimolecular concentrations" is comprised of. It is unclear if this "bimolecular concentration" refers to a protein/cell volume, or DNA/cell volume or other parameter per cell volume. It appears from the specification that "bimolecular concentration" is affected by the interaction of protein and DNA (page 11, lines 9-13).

6. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining the percentage of G2 cells in homogenous population of cells using a laser biocavity comprising a semiconductor material and a method for determining the concentration of hemoglobin in an erythrocyte within a blood sample, does not reasonably provide enablement for a method of determining the G2 phase of cells in a

heterogeneous population of cells, a method of determining the biomolecular concentration within a cell, or a method of detecting cancer from a sample of cells taken from an individual. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is noted that the limitation of "having a semiconductor laser" has been dropped from the claims, which not read on a the "laser biocavity" without having the limitation of comprising a semiconductor. Thus, the claims encompass any laser biocavity incorporating any material. Applicant argues on page 15 of the response that the gain media of the biocavity can include gas, organic dye, solid state and semiconductor gain media. This has been considered bout not found persuasive. The specification teaches on page 3, lines 22-24 that "the semiconductor laser is the enabling component of this microanalysis system because of its ability to emit coherent, intense light from a small aperture compatible with the dimensions of a human cell". Thus, the argument that the specification is enabling for the incorporation of other gain materials within the biocavity laser through reliance on the teachings of US 5,793,485 is unpersuasive because the instant specification states that it is necessary to have semiconductor gain material within the biocavity.

Claims 1-3 are drawn to method of detecting cancer using a laser biocavity including a microchannel through which cells in fluid traverse, wherein said method comprises determining the laser wavelength shift of the biocavity when each cell passes through, followed by the determination of the percentage of cells in the G2 phase from the wavelength shift of the cells, wherein an increased percentage of G2 phase cells is indicative of cancer. Claim 2 specifically includes the limitation of determination of the cell phase of G0, G1, S, G2 and M. However, the specification has not taught how to use the laser biocavity to discern between cells of the same type, for example, astrocytes, which are in the G0, G1, S, G2 or M phase. The specification teaches that the G2 cell is evident from a G0, G1, S or M cell or the same type because the G2 cell contains the replicated chromosomal material and thus is haploid because it comprises 4X of the number of chromosomes rather than 2X which would be present in G0 and G1. The specification has not taught how to discern G0 from G1 on this basis. Neither has the specification taught how to differentiate the S phase of the cell cycle in which the chromosomal

material is being duplicated and therefore somewhere in between 2X and 4X, and the M phase in which the cell is drawing apart into two daughter cells, the DNA content of the parent cell changing from 4X to 2X, as the M phase progresses. Thus, while enabling for the detection of a percentage of homogenous cells in G2 phase, such as a cell culture, the specification is not enabling for the discernment of the individual phases of the cell cycle.

Claim 4 is drawn to a method of determining the phase of cells in the cell cycle comprising determining the wavelength shift of the biocavity when a cell passes through the microchannel and determining the phase of the cell based on the wavelength shift. Claim 5 embodies the method of claim 4 wherein the wavelength shift is determined for a plurality of cells, and the relative number of cells in the G1 and G2 phases are determined, wherein greater than 2% of cells in the G2 phase is indicative of cancer.

Claim 6 is drawn to a method of determining bimolecular concentration comprising determining by means of a wavelength shift in a laser biocavity the biomolecular concentration of the cell. Claim 7 embodies the method of claim 6 wherein a ratio of cells in G2 phase versus non-cancerous cells in G2 phase is determined.

Claim 8 is drawn to a method of detecting an increased growth rate comprising determining a shape of a first wavelength distribution of a combined G1 and S phase cell distribution to provide measurement of a cell growth rate. Claim 8 embodies the method of claim 7 wherein the first and second wavelength distributions are integrated and the ratio determined to provide a measurement of a cell growth rate. It is noted that neither the claims nor the specification provide an explanation for how the growth rate of a single cell "a cell growth rate" can be inferred from measurements on populations of cells.

The claims are broadly drawn to encompass the detection of cancer or the determination of the ratio of G1 to G2 in a sample taken from an in situ tumor, as well as the determination of the cell cycle in a homogenous population of cells, or tumor cells, such as cell in culture. The specification is not enabling for the detection of cancer from a sample taken from an in situ tumor or the determination of the phase of cells in the cell cycle from a sample taken from an in situ tumor. It is further noted that all types of cancers are included within the scope of the claims.

It is well known in the art that one of the major pitfalls for the analysis of the cell cycle in samples obtained in vivo is the frequent absence of pure cell populations, and that more often than not a mixture of different cell types exist at variable proportions which may present a different distribution along the distinct cell cycle phases, and thus it follows that the global analysis of the cell cycle in such samples does not provide direct information on the proliferation of each of the different subpopulations present in the sample (Orfao de Matos Correia e Vale, EP 798, 386, column 1, lines 36-45, cited in the previous Office action).

The art teaches that there are numerous lasing modes for a transparent object within a biocavity semi-conductor laser (Meissner et al, SPIE, 1995, Vol. 2399, pp. 561-570, figure 8, cited previously). The art teaches that the nuclei of placental spindle cell tumor gave off a pattern of emitted light that was complex (Gourley, Nature Medicine, 1996, Vol. 2, pp. 942-944, page 943, figure 3, "spindle nuclei modes", cited previously), and that this pattern represents DNA/protein interactions within the cell (Gourley, Optics and Photonics News, 1997, Vol. 8, pp. 31-36, page 33, first column, lines 11-13 under the heading "Physics of the biological microcavity laser", cited previously) . One of skill in the art would reasonably conclude that the laser spectrum of a range of different tumor cells derived from a sample taken from a patients would be complex and unpredictable due to the inherent heterogeneity of tumor cells with regard to ploidy and DNA/protein interactions. Thus, one of skill in the art would be subject to undue experimentation with regard to identifying which peak is G1 and which peak is G2. With regard to the acquisition of laser spectra from a population of cells, the art also teaches that when a population of cells are examined the pulse output will vary from cell to cell, and the spectrum will be a composite of distinct single cell spectra comprising a peak near h=0 with other peaks at higher pulse heights, and that the number of these peaks will depend on the number of distinct cell types that dominate the distribution. (Gourley, Sandia National Laboratories Technical Report, 1997 (SAND97-1988), pp. 1-26, especially page 18, second full paragraph, cited previously). Thus, one of skill in the art would expect a complex laser spectrum from every unique sample. Further, claim 5 requires that the determination of the relative number of G1 and G2 phase cells is by means of the "number of data points grouped about distinct values of wavelength shift" which for the reasons set forth under 12, second paragraph above, cannot be determined. Further, the specification states on page 11, lines 19-21 that "It

remains an open question if the total biomolecular content measurement of a biocavity laser is able to detect cancer in an individual cell. Such a measurement would have to detect differences in the cells that are unique to cancerous cells", thus confirming the statements made by the examiner in the previous Office action regarding lack of enablement for the detection of cancer.

7. Applicant argues that the complexity of the laser spectrum from each cell type is an advantage for the identification of both the cell type and the phase of the cell within the cell cycle for a particular cell types origination in a heterogeneous sample. Applicant argues that it is customary in molecular spectroscopic analysis of heterogeneous samples to employ the simultaneous behaviors of the number of spectral wavelengths originating from the same molecule to distinguish it between the different molecular constituents in the heterogeneous sample. This has been considered but not found persuasive. Firstly, complex spectrum can be an advantage as a "fingerprint" enabling the discernment of a specific cell type within a mixture, However, the complex spectrum necessarily must have been already recorded and attributed to the cell in question. One of skill in the when confronted with said complex spectrum would not be able to identify said cell type unless the fingerprint was already known for said cell type. Secondly, the instant invention requires the identification of the wavelength shift that representing G2 for a population of cells. For the reasons stated above, it would not be expected that the G2 peak would occur at the same wavelength for every cell given that the claims encompass all cell types and all cancer types and the protein DNA ratios for all the cells in question would not e expected to be the same and further, cancer cells within a given type of cancer, such as breast cancer, contains abnormal amounts of chromosomal materials because of chromosomal instability therefore it would be impossible to identify the peak attributed to the G2 wavelength shift without a control cell for every cancer cell within the population. Further, tumors are comprised of a mixture of cell types both malignant and non-malignant, for example cervical carcinomas comprise squamous cells intermixed with malignant epithelial cells surrounding non-malignant epithelial cells. The squamous cells would have DNA protein ratios that would not be expected to be the same as the DNA protein ratios in the cervical columnar cells because they are from completely different cells types. Further, the malignant cells within the tumor having chromosomal instability would vary in DNA content. Given the lack of

teachings in the specification, one of skill in the art would not be able to identify the G2 peak for any cell within a tumor mass without previously having had the same cells as a known cell within the laser biocavity.

Applicant argues that in US 5,793,485 the biocavity laser was used to measure the optical spectra of cells and to identify the particular type of cell by analyzing the wavelength information, the laser mode separation and the intensity. This has been considered but not found persuasive. '485 patent disclosures lasing emission spectra from normal erythrocytes of different sizes (column 18, line 21 to column 19, line 25) versus the lasing emission obtained from sickled red blood cells (column 19, line 47 to 48) It is well known in the art that erythrocytes are enucleated cells. Thus, the method of '485 would not require the detection of a G2 peak because the erythrocytes have no genomic DNA. In a sample of blood cells, all other cells such as lymphocytes and monocytes have genomic DNA. It is noted that the '485 patent teaches that the lasing emission spectrum of the sickled cells is complicated due to the large size of the cell (column 20, lines 30-33). Further the '485 patent teaches that "White blood cells are much more complex than red blood cells. White blood cells are larger, vary in shape, and contain a nucleus and other smaller organelles within the cytoplasm. In addition there are several different types of white blood cells classed as polymorphonuclear leukocytes (including polymorphonuclear neutrophils, polymorphonuclear eosinophils, and polymorphonuclear basophils), lymphocytes, and monocytes. This complexity leads to lasing images and spectrum as measured by the apparatus 10 that are rich in structure. Whereas, an entire red blood cell can support lasing, a white blood cell generally only supports lasing in the condensed matter of the nucleus or in the peripheral region outside the nucleus bounded by the cell membrane. In addition, the nucleolus and some larger complexes outside the nucleus can also support lasing. Lasing modes in two common types of white blood cells are described hereinafter" Thus, this serves to demonstrate that even a pathological cell would exhibit lasing emission that would radically differ from normal cells. Further, there is not a great deal of heterogeneity between erythrocytes but there is a great deal of heterogeneity between cancers cells of the same type and within the same tumor. It would be expected that the erythrocytes would different in cell volume and amount of hemoglobin comprised within because without the presence of genomic DNA erythrocytes are not manufacturing proteins. The resulting spectrum generated from a erythrocyte within a laser

biocavity would be a "fingerprint" of a erythrocyte. One of skill in the art would not be subject to undue experimentation by having to have a control erythrocyte for every different erythrocyte within the sample because it would be expected that there would be relatively little variation between erythrocytes within a blood sample and between erythrocytes between different individuals. This is not the fact pattern of the instant invention. Cancer cells differ from other types of cancer cells. Cancer cells differ from other cancer cells of the same type within the same tumor and between individuals, and tumor cells differ in the types of non-malignant cells that are par of said tumor. It would be necessary to have control cells within the G2 phase for every type of tumor cells detected in order to localize the G2 wavelength shift. One of skill in the art would e subject to undue experimentation without reasonable expectation of success in order to practice the instant method.

8. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A)As drawn to written description of the claimed invention

The instant claims are reliant upon a genus of biocavity lasers. The specification provides a written description of a laser cavity having the dimensions of a cell wherein one surface is a semi-conductor. The disclosure of the specific semi-conductor laser does not adequately describe all other possible materials which could be used in the laser surface. One of skill in the art would reasonably conclude that applicant was not in possession of a genus of biocavity lasers. It logically flows that if the specification lacks adequate written description for the structure of the laser on which the claimed methods depend, the claimed methods also lack adequate written description.

Applicant argues that the prior application which is incorporated by reference teaches that gas, organic dyes and solid state gain material can be used in the biocavity laser. This has been considered but not found persuasive. The specification teaches on page 3, lines 22-24 that "the semiconductor laser is the enabling component of this microanalysis system because of its ability

to emit coherent, intense light from a small aperture compatible with the dimensions of a human cell". Thus, the argument that the specification is enabling for the incorporation of other gain materials within the biocavity laser through reliance on the teachings of US 5,793,485 is unpersuasive because the instant specification states that it is necessary to have semiconductor gain material within the biocavity. Thus the description of a semiconductor biocavity laser does not describe a genus of biocavity lasers because gas, organic dyes and solid state gain material would not be expected to have functional attributes of the gain material required in the instant method.

(B) As drawn to new matter

Claim 5 embodies the method of claim 4, wherein determining whether the ration of the number of the cells in the G2 phase to the number of cells in the G1 phase[s] is greater than 0.02 to provide an indication of cancer. The specification asserts on page 9, lines 13-18 that for a population of normal human astrocytes, 2% of the total cells in G2 phase is consistent with normal cell replacement. However, this observation with regard to one specific cell type does not provide adequate written description of a method wherein greater than 2% of the total number of cells in G2 phase is indicative of cancer, because the disclosure of a single species of cell type, such as an astrocyte, does not adequately describe the genus of cells which encompasses "cancer" cells which include lymphocytes, fibrocytes, squamous cells, hepatocytes, epithelial cells, etc.

9. All other rejections and objections as set forth in the previous Office action are withdrawn.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

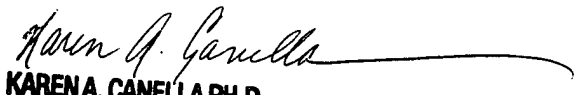
will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
7/27/2004



KAREN A. CANELLA PH.D
PRIMARY EXAMINER